- - 41. A method for the production of a mutant high alkaline protease, said method comprising the steps of:

a) obtaining a non-reverting alkalophilic Bacillus host incapable of producing a wild-type high alkaline protease, wherein said Bacillus host comprises an integration cassette comprising a gene encoding said mutant high alkaline protease; and

b) growing said Bacillus host under conditions whereby said mutant high alkaline protease is expressed.

42. The method of Claim 41 further comprising the step of isolating said mutant high alkaline protease.

43. The method of Claim 41 wherein said alkalophilic Bacillus host is an asporogenic alkalophilic Bacillus strain.

44. The method of Claim 41 wherein said alkalophilic Bacillus strain is a Bacillus novo species PB92 or a derivative thereof said derivative retaining characteristics of the parent strain.

45. The method of Claim 41 wherein said wild-type protease gene has been deleted by homologous or illegitimate recombination.

46. The method of Claim 41 wherein said integration cassette is contained in a plasmid.

47. The method of Claim 41 wherein said integration cassette is integrated into the genome of said alkalophilic Bacillus host.

48. A method of obtaining a non-reverting alkalophilic Bacillus strain having a reduced level of extracellular high alkaline protease, said method comprising the steps of:

a) transforming an alkalophilic Bacillus strain comprising a wild-type high alkaline protease gene with a cloning vector comprising DNA encoding a

replication function and 5' and 3' flanking non-coding regions of said high alkaline protease gene but not the coding region of said high alkaline protease gene, wherein a sufficient amount of said 5' and 3' flanking non-coding regions is present to provide for homologous recombination with said wild-type high alkaline protease gene whereby transformants having a reduced level of high alkaline protease are obtained;

b) growing said transformants under conditions whereby the replication function encoded by said cloning vector is inactivated; and isolating transformants having a reduced extracellular alkaline protease level.

49. The method of Claim 48 wherein said alkalophilic Bacillus strain is Bacillus novo species PB92 or a derivative thereof said derivative retaining characteristics of the parent strain.

50. An alkalophilic Bacillus strain producing a mutant high alkaline protease and no detectable wild-type extracellular high alkaline protease, wherein said Bacillus strain is obtained by growing an alkalophilic Bacillus strain which is incapable of producing said wild-type high alkaline protease transformed with a plasmid expression vector comprising said mutant high alkaline protease gene.

51. The alkalophilic Bacillus strain of Claim 50 wherein said strain is Bacillus novo species PB92 or a derivative thereof said derivative retaining characteristics of the parent strain.

52. The alkalophilic Bacillus strain of Claim 50 wherein said strain is a non-reverting strain.

53. The alkalophilic Bacillus strain of Claim 50 wherein said strain is asporogenic. - -

REMARKS

This application has been pending for almost 8 years having been filed August 10, 1990. Applicants learned through discussion with the USPTO Petitions Branch,

specifically Byron Hearn, that the instant application became abandoned unintentionally when a Response pursuant to 37 C.F.R. 1.129 was submitted after the filing of an Appeal Brief mailed March 2, 1994. Despite the submission being in conflict with the requirements of 37 C.F.R 1.129, the Response was accepted by the USPTO and prosecution continued for an additional three years.

Pursuant to the instruction of the Petitions Branch, Applicants submit concurrently herewith a Petition to Revive Unintentionally Abandoned Application and a Petition under 37 C.F.R. 1.183 to waive the rules regarding a Response under 37 C.F.R. 1.129.

Applicants have canceled Claims 4-7, 9-10, 12-14, 19, 23-25, 29-35 and 38-40, without prejudice and have substituted therefore, Claims 41-53. Applicants reserve the right to prosecute any subject matter canceled by the instant amendment in related applications.

Basis for Claim 41 can be found throughout the specification and in particular at the following pages:

method for production of mutant Bacillus protease	page 4, lines 14-17 page 6, lines 17-26
mutant high alkaline protease	page 10, lines 11-14
non-reverting host	page 7, line 17
alkalophilic Bacillus host	page 4, lines 34-35; page 6, lines 11-13 page 7, lines 6-8
integration cassette	page 4, lines 23-26
growing said host . . .	page 4, line 30-32.

Support for Claim 42 can be found at page 15, lines 1-5; support for Claim 43 can be found at page 4, line 19 and page 6, lines 12; support for Claim 44 can be found at page 12, lines 8-10; support for Claim 45 can be found at page 7, lines 20-22 and page 9, lines 15-18; support for Claim 46 can be found at page 8, line 25; support for Claim 47 can be found at page 4, lines 26-28; support for Claim 48 can be found throughout the specification and in particular at page 8, lines 11-24 and the paragraph bridging pages 8 and 9; support for Claim 49 and 51 can be found at page 12, lines 8-10; support for

claim 50 can be found at page 6, lines 10-26; support for Claim 52 can be found at page 7, lines 17; support for Claim 53 can be found at page 4, line 19 and page 6, line 12.

I. **The Claims Are Enabled**

The Office Action rejects Claims 4-7, 9-10, 12-14, 19, 23-25, 29-35 and 38-40 under Section 112, first paragraph. The Office Action states that the disclosure is enabling only for claims limited to methods of producing an alkalophilic asporogenic Bacillus novo species PB92 of minimal natural extracellular protease level, transformed with Bacillus PB92 alkaline protease.

Applicants respectfully traverse the Section 112, first paragraph rejection of the claims as they apply to the currently pending claims. Preliminarily, Applicants point out that MPEP sections 706.03(n) and 706.03(z) which were referenced by the Office Action have been deleted from the sixth edition of the M.P.E.P. and invite the Examiner to clarify this oversight.

A. Applicants believe that the USPTO has not met their burden of showing a prima facie case of non-enablement of the claimed invention.

It is well established that to be enabling, the specification need only provide sufficient information to allow one *skilled in the art* to make and use the invention without undue experimentation. Scripps Clinic & Research Found. V. Genentech, Inc., 927 F.2d 1565, 18 U.S.P.Q. 2d 1001, 1006 (Fed. Cir. 1991). Applicants believe that they have provided sufficient information to teach one of skill in the art how to make and use the invention and believe that the USPTO has not met their burden of showing adequate grounds for non-enablement of the claimed invention.

As the Office Action accurately states, a number of factors must be considered in assessing the enablement of an invention including the breadth of the claims, the examples provided, the level of skill in the art, and the nature of the invention. In re Wands, 8 USPQ2nd, 1400 (Fed. Cir. 1988). Applicants submit that the Office Action does not provide reasonable grounds for doubting the objective truth of the statements within the instant specification.

The instant Office Action states at page 2 that the Section 112, first paragraph rejection of claims is not merely a matter of breadth and further states that the

"Examiner and Patent Office does not possess the facilities to test and screen other Bacillus strains and high alkaline protease genes ". Applicants note that based on the Court's holding in In re Wands this is clearly not an appropriate test for Section 112, first paragraph compliance and the USPTO has not met their burden of providing a reasonable doubt of the objective enablement based on this test. The Court held that the test is not whether the USPTO is required to "test and screen" but whether the specification teaches any person skilled in the art to make and use the invention.

The Office Action further states at page 3 that

> "Applicants must be asserting that their invention teaches one of skill in the art how to isolate, produce and utilize any high alkaline protease gene from any Bacillus strain"

suggesting that compliance with Section 112, first paragraph requires such teachings. Applicants submit that requiring disclosure of all possible embodiments of an invention *is not* an appropriate test for enablement under In re Wands. In fact, the specific nucleic acid sequence of the high alkaline protease is irrelevant to the claimed invention. As held by the courts in Texas Instr. Inc. v United States ITC (231 USPQ 833, Fed. Cir. 1986) compliance with Section 112, first paragraph does not require that an applicant describe in the specification every conceivable and possible future embodiment of his invention.

The Office Action states that the level of skill in the art regarding cloning of genes was high (see Office Action page 3, line 13) suggesting that the use of cloning tools, i.e. tools for cloning alkaline protease genes and transforming bacterial hosts with the cloned genes, were deemed routine. Applicants are concerned that the USPTO persists in maintaining their allegation of lack of enablement based upon the fact that the present invention falls within an unpredictable art area. As held in Ex parte Goeddel, mere broad generalizations and allegations are insufficient for a holding of non-enablement. As stated:

> The ultimate question in each case manifestly is whether or not it contains sufficiently explicit disclosure enabling the average routineer in the field to practice an invention claimed therein. (In re Goeddel, 5 USPQ2d 1449 (Bd. Pat. App. & Int'f 1987).

Applicants believe that the USPTO has not met its burden of providing reasonable doubt of the objective enablement of the claimed invention.

B. The Claims ar Enabled.

Applicants assert that they have taught how to make and use the presently claimed invention and that no undue experimentation would be required to practice it.

The presently claimed invention provides that mutant high alkaline protease can be produced in a recombinant Bacillus host and in the absence of contamination with wild type protease by using as a host strain an alkalophilic Bacillus strain that is incapable of producing its wild-type protease and wherein the strain is incapable of reverting back to the wild-type genotype. The presently claimed invention is directed to methods for the production of mutant high alkaline protease, methods of obtaining non-reverting alkalphilic Bacillus strains and alkalophilic Bacillus strains for use in the methods.

The present specification teaches how to make and use a non-reverting alkalophilic Bacillus host cell at page 7, lines 17-38 through page 9, lines 1-26; and page 10, lines 3-10. The present specification teaches how to make and use mutant high alkaline protease at page 13, lines 1-16 and in Example 3. Specific mutant proteases are disclosed at page 23, lines 19-24 (M216Q, M216S, S160D and N212D) and strains PEP111 and PEP112 containing the mutated protease genes M216Q and M216S, respectively, are disclosed at 26, lines 33-36 and page 27, lines 1-3. Cloning and transformation techniques are disclosed at page 7, lines 12-27; at page 9, lines 26-38 through page 10, lines 1-2; page 13, lines 17-38; page 14, lines 1-38; and in particular, transformation techniques for alkalophilic Bacillus strains are disclosed at page 14, lines 23-25. High alkaline proteases are described at page 10, lines 11-20. Alkalophilic Bacillus are described at page 10, lines 21-33. Mutant alkaline proteases are described at page 13, lines 8-16.

Moreover, it is well established that a patent need not disclose what is well known in the art and thus available to the public. Applicants submit that high alkaline proteases, as well as the tools necessary for mutating, cloning and transforming genes were well within the skill of those in the art as of the effective priority date of the present invention. This point has been conceded by the Examiner.

A variety of high alkaline proteases were known by those of skill in the art as of the filing date of the instant application. As the Examiner has stated in the Office Action mailed July 15, 1992, Tenijenhuis discloses a purified high alkaline protease from

Bacillus novo sp. 92. Tenijenhuis also states at col. 1, lines 20-27 that enzymes with high activity in alkaline media are described in several other references including British patent No. 1,243,784 and Dutch patent Application No. 72.07050. High alkaline proteases were also described in U.S. patent 3,723,250; U.S. patent 4,480,037; U.S. patent 3,905,869; and U.S. patent 4,052,262. Examples of alkalophilic Bacillus strains and the proteases derived from them are also described in Hiroski (1982, Alkalophilic Microorganisms, Springer Verlag, New York).

In spite of the explicit teachings provided by the specification and the knowledge available to the skilled artisan at the effective priority date of the present invention, the USPTO alleges that the present specification is enabling *only* for claims limited to the illustrative examples, i.e., methods of producing an alkalophilic asporogenic Bacillus novo species PB92 of minimal indigenous extracellular protease level, transformed with a mutated B. novo PB92 alkaline protease described in the specification. Applicants appreciate that the USPTO concedes that the illustrative examples are enabling, but believe that the claims should not be limited only to embodiments described in the illustrative examples.

In fact, it is well settled that claims need not be limited to illustrative examples or preferred embodiments in order to satisfy enablement requirements. The CCPA emphasized that:

> To demand that [Applicant] shall limit his claims . . . to materials which meet the guidelines specified for "preferred" materials in a process . . . would not serve the constitutional purpose of promoting progress in the usefull arts, see In re Goffe, 191 U.S.P.Q. 429, 431 (CCPA 1976).

Applicants assert that the average routineer in the field following the explicit teachings of the present specification would be able to practice the presently claimed invention without undue experimentation.

The Office Action mailed April 1, 1997 states at page 3, lines 19-21 that:

> ". . . the specification is not enabled for the phrase "mutated high alkaline protease". The predictability of the results of such random and non-specific mutations is extremely low, as well as the experimental level for such random mutation is very high."

Applicants respectfully assert that the phrase "mutated high alkaline protease" is explicitly described in the specification, at page 13, lines 8-16. It is also respectfully submitted that the USPTO has gone on record as stating that preparing mutants of known proteases would be well within the ordinary skill in the art and not require undue experimentation, see the Office Action mailed September 24, 1991, page 8, lines 23-25 and page 9, line 1. The Office Action challenges the predictability of the results, i.e., activity, of mutation of proteases, however this question is irrelevant to the presently claimed invention. There is no recitation that the mutations have a higher, lower or equivalent reaction rate as the wild-type protease, see the specification at page 13, lines 8-16. The presently claimed invention only requires that the host cell will produce the mutant protease.

The instant Office Action states at page 4, lines 2-4 that based on the claimed invention, one skilled in the art would have to master all facets necessary for two different high alkaline protease genes, not just one (presumably because the claims recite wild-type as well as mutant proteases), and concludes that therefore, the amount of experimentation would be doubled.

Section 112, first paragraph requires that the specification must enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention without any undue experimentation. It is not fatal if some experimentation is required. Applicants don't concede that the amount of experimentation would be "doubled" for one of skill in the art to practice the claimed invention. Assuming arguendo that this statement were correct, this still would not affect compliance with Section 112, first paragraph if the experimentation were not undue.

The instant Office Action states that the specification is not properly enabled for claims to any Bacillus novo species PB92 derivative. Applicants submit that derivative strains are fully enabled by the instant specification and invite the Examiner's attention to page 16, line 32 which discloses PBT110, a PB92 derivative and page 18, lines 9-14, which discloses PBT 125 and PBT 126 both protease negative, asporogenic strains. In order to expedite prosecution, Applicants have amended the claims which refer to derivative strains, Claims 44, 49 and 51, to recite that the derivative strain retains characteristics of the parent strain.

Applicants point out that the Office Action concedes that the specification has provided an enabling example of the claimed invention (see the Office Action page 5, lines 6-10). As Applicants have pointed out, various high alkaline proteases, as well as various alkalophilic Bacillus, were known in the art at the effective priority date of the present invention. Cloning techniques were deemed routine to those of skill in the art and transformation techniques for alkalophilic Bacillus were disclosed in EP-A-0283075. The Examiner and Applicant both believe that preparing mutants of proteases was well within the skill in the art.

In view of the above arguments, Applicants believe that the currently pending claims are enabled and respectfully request that the Section 112, first paragraph rejection of Claims 4-7, 9-10, 12-14, 19, 23-25, 29, 30-35 and 38-40 and as the rejection might apply to the currently pending Claims 41-53, be withdrawn.

II. **Rejection of Claims 38 under Section 112, 2nd**

The Office Action has rejected Claim 38 based on the use of the phrase "In Detergent Composition". Applicants have amended the claim set to eliminate the use of the objected phrase thereby obviating this rejection.

III. **Rejection of Claims under Section 103**

The Examiner has rejected Claims 19, 24-25 and 38-40 under Section 103. Applicants have canceled without prejudice all claims relating to detergent compositions thereby mooting the Examiner's Section 103 rejection. Applicants reserve the right to prosecute all canceled subject matter in related applications.

CONCLUSION

Applicants acknowledge the Examiner's statement that Claims 4-7, 9-15, 23 and 26-34 are free of the prior art. In view of the amendments to the claims and the remarks

provided herewith, Applicants submit that this application is in condition for allowance. Such action by the Examiner is earnestly solicited.

Respectfully submitted,

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